In the Office Action dated February 7, 2002, all of the pending claims (claims 24-30, 32-37, 39-41, and 43-87) were finally rejected. Applicants note that claim 38 was withdrawn from consideration, as drawn to a nonelected invention. Accordingly, applicants have cancelled this claim herein solely for this reason.

The Office maintained the rejection of claims 24-30, 32-37, 39-41, and 43-46, under 35 U.S.C. § 103(a), as obvious over Makino in view of Mills, Sekizaki, Naddif, and Ozenberger. (Office Action at 2.) This rejection was also newly applied to claims 47-87. (*Id.*) Applicants note that this rejection is moot as applied to claims 24-35, 38, 47, and 50-87, because these claims have been cancelled. Applicants respectfully traverse the stated basis for this rejection as applied to claims 36, 37, 39-41, 43-46, 48, and 49.

The pending claims all recite *Shigella* comprising "an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene." The claims also all recite that the thus mutated *Shigella* are "defective in spread within infected cells and from infected to uninfected cells of the host." None of the cited references disclose either (1) an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene; or (2) a *Shigella* that is defective in spread within infected cells and from infected to uninfected cells of the host. Further, none of the cited references discloses a motivation to combine its teachings with those of any of the other cited references to arrive at a *Shigella* that meets both of these requirements of the pending claims. Accordingly, the claims are nonobvious over the cited references.

More particularly, Makino discloses that a region on the large virulence plasmid of *Shigella* is required for cell-cell spread of the bacterium. (*See* Makino, abstract.)

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Makino refers to this region as virG. The instant application and the pending claims refer to a gene encoded by this region as the *icsA* gene.

Makino also discloses that a mutant *Shigella*, comprising a virG/*icsA* gene that is inactivated by means of a transposon inserted into the gene, invades host cells and multiplies within host cells, "but do[es] not proceed further." (Makino at page 554, left column.) The Office's position is that these disclosures of Makino teach all elements of Applicants' claims, other than Applicants' use of a method of mutagenesis that is different than that of Makino. (*See, e.g.*, Office Action at 5.) Specifically, Makino discloses a virG/*icsA* gene that is inactivated by means of a transposon inserted into the gene, while Applicants' claims, in contrast, encompass an *icsA* gene inactivated other than only by means of a transposon inserted into the gene. Clearly, the genus of *icsA* mutants of Applicants' claims and the genus of *icsA* mutants taught by Makino are entirely distinct from each other. The Office contends that the other cited references remedy this deficiency of Makino. Applicants disagree for all of the reasons stated in their previous Response.

Makino likewise fails to disclose a *Shigella* that is defective in spread within infected cells and from infected to uninfected cells of the host, as required by Applicants' claims. Makino observes that their VirG/*icsA* mutant "can multiply in the epithelial cells *in vitro* but are extinguished before they can spread and infect adjacent cells." (Makino at page 551, right column.) Makino also notes that, "[a]lthough multiplication occurs, the bacteria lack active movement, show a tendency to localize within the cytoplasm, are gradually converted to a spherical morphology, and are finally extinguished from the epithelia." (Makino at page 554, left column.) Makino proposes

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

three possible explanations for these observations: "First, the phagosome membrane may not be destroyed in these mutants. Second, these bacteria may have lost the ability to resist lysosomal bactericidal enzymes. Or [third,] they may have lost a factor required for normal growth within the epithelium." (Makino at page 554, left column.) Finally, Makino concludes that "the function of the virG gene product is to resist somehow the bactericidal activity of lysosomal enzymes." (Makino at page 554, left column.)

Applicants submit that resistance, somehow, of the bactericidal activity of lysosomal enzymes is not the same as spreading within infected cells and from infected to uninfected cells of a host. Thus, a disclosure of a *Shigella* mutant with the inability to resist the bactericidal activity of lysosomal enzymes is not a teaching of *Shigella* that are defective in spread within infected cells and from infected to uninfected cells of the host, as recited in Applicants' claims.

Accordingly, in view of the teachings of Makino, taken as a whole, one of skill in the art would have concluded that the reason why virG/*icsA* mutants are defective in cell-cell spread, as indicated in the abstract, is that the mutants are easily destroyed following entry of host cells, because the mutants are defective, somehow, in resistance to the bactericidal activity of lysosomal enzymes of the host. This is not a disclosure of a *Shigella* mutant that is both defective in spread within infected cells and defective in spread from infected to uninfected cells of the host, as required by Applicants' claims. In addition, Makino no where provides a motivation to modify its teachings so as to arrive at a Shigella mutant that is both defective in spread within infected cells and defective in spread from infected to uninfected cells of the host.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

None of the other cited references provides a motivation to modify the teachings of Makino, or even discloses how any such modification could be made, in order to arrive at a mutant *Shigella* that is both defective in spread within infected cells and defective in spread from infected to uninfected cells of the host. For these reasons the cited references cannot render the claims obvious and the rejection under 35 U.S.C. § 103(a) should be withdrawn.

The Office also newly rejected claims 58-73 and 82-87 under 35 U.S.C § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time that the application was filed. (Office Action at 7.) Applicants submit that this rejection is moot because these claims have been cancelled.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 36, 37, 39-41, 43-46, 48, and 49 in condition for allowance. Applicants submit that the proposed amendments of claims 36 and 41 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: August 7, 2002

By: _____
Kenneth J. Meyers
Reg. No. 25,146

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com